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The Synthesis and Reactions of 7-Carboxy Isatoic Anhydride

Elsa M. Janle

The Synthesis and Reactions of 7-Carboxy Isatoic Anhydride

by Elsa M. Janle

This paper is submitted to the faculty of Ursinus College in partial fulfillment of the requirements for departmental honors in chemistry.

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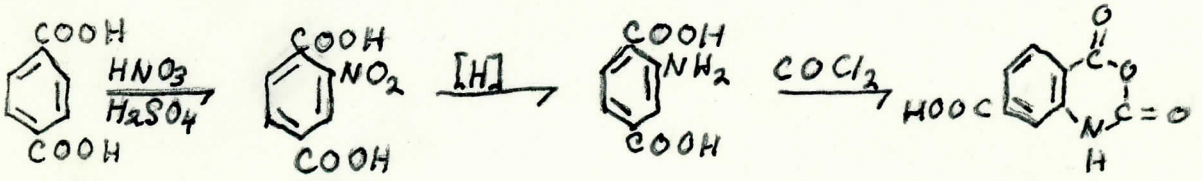
Introduction

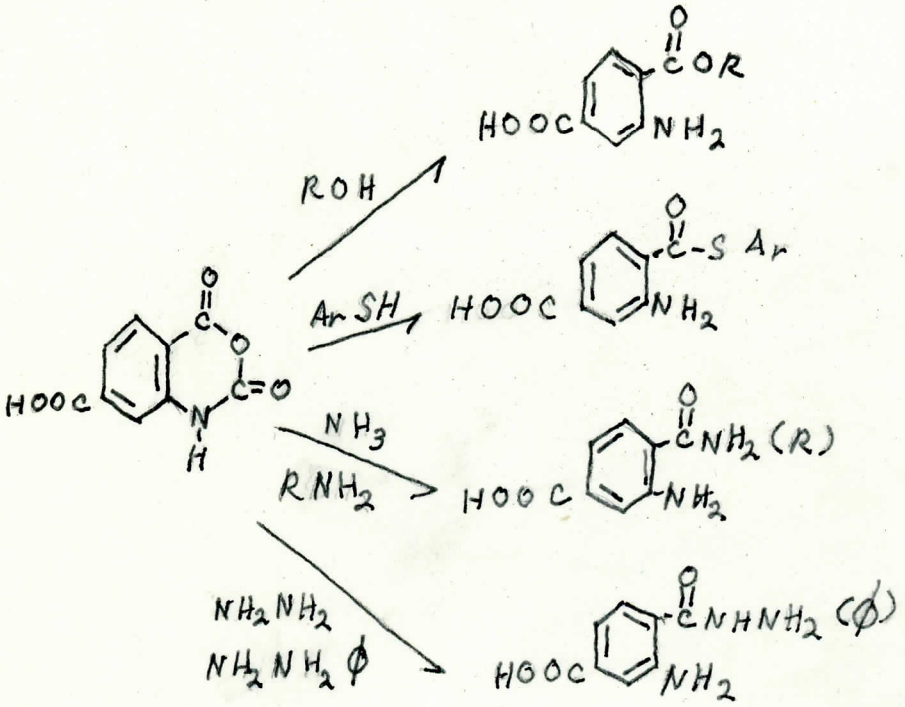
The object of this research project was the preparation and characterization of 7-carboxy isatoic anhydride and the study of the reactions of this compound of new composition.

The proposed path of synthesis was the nitration of terephthalic acid, reduction of the nitro group to form amino-terephthalic acid, and ring closure with phosgene to the desired 7-carboxy isatoic anhydride by the following scheme:



The preparation of both nitro[1] and amino terephthalic acid[2] have been reported in the literature. Terephthalic acid, however, was chosen as a starting material because it was commercially available and relatively inexpensive.

Upon confirmation of synthesis and characterization of 7-carboxy isatoic anhydride, investigations of the reactions showed it to undergo ring cleavage when attacked by various nucleophiles in a manner very similar to the reactions of the unsubstituted isatoic anhydride.[3] It has been established that 7-carboxy isatoic anhydride reacts with ammonia and aliphatic and aromatic amines to form 2-amino-4-carboxy-benzamides; with alcohols to form the 2-amino-4-carboxy benzoates; with thio phenols to form the 2-amino-4-carboxy thio benzoates; and with hydrazine and phenyl hydrazine to form the 2-amino-4-carboxy benzhydrazides as outlined in the following reaction scheme:



These products are compounds of new composition and are characterized for physical properties and confirmed by analysis. Infra red spectra are available for each chemical entity.

Synthesis of 7-Carboxy Isatoic Anhydride

Preparation of Nitro terephthalic acid

Nitro terephthalic acid was prepared according to the procedure described in Beilstein[4,5] with a few minor modifications. Although the Beilstein procedure uses 20 grams of terephthalic acid, the preparation was first tried with only two grams because other references[6] state the reaction tends to become explosive if more than two grams of terephthalic acid are nitrated. This explosive nature of the reaction was not observed, and when such small quantities were used the reaction mixture did not become warm. Therefore the amount of terephthalic acid nitrated was gradually increased to 20 grams.

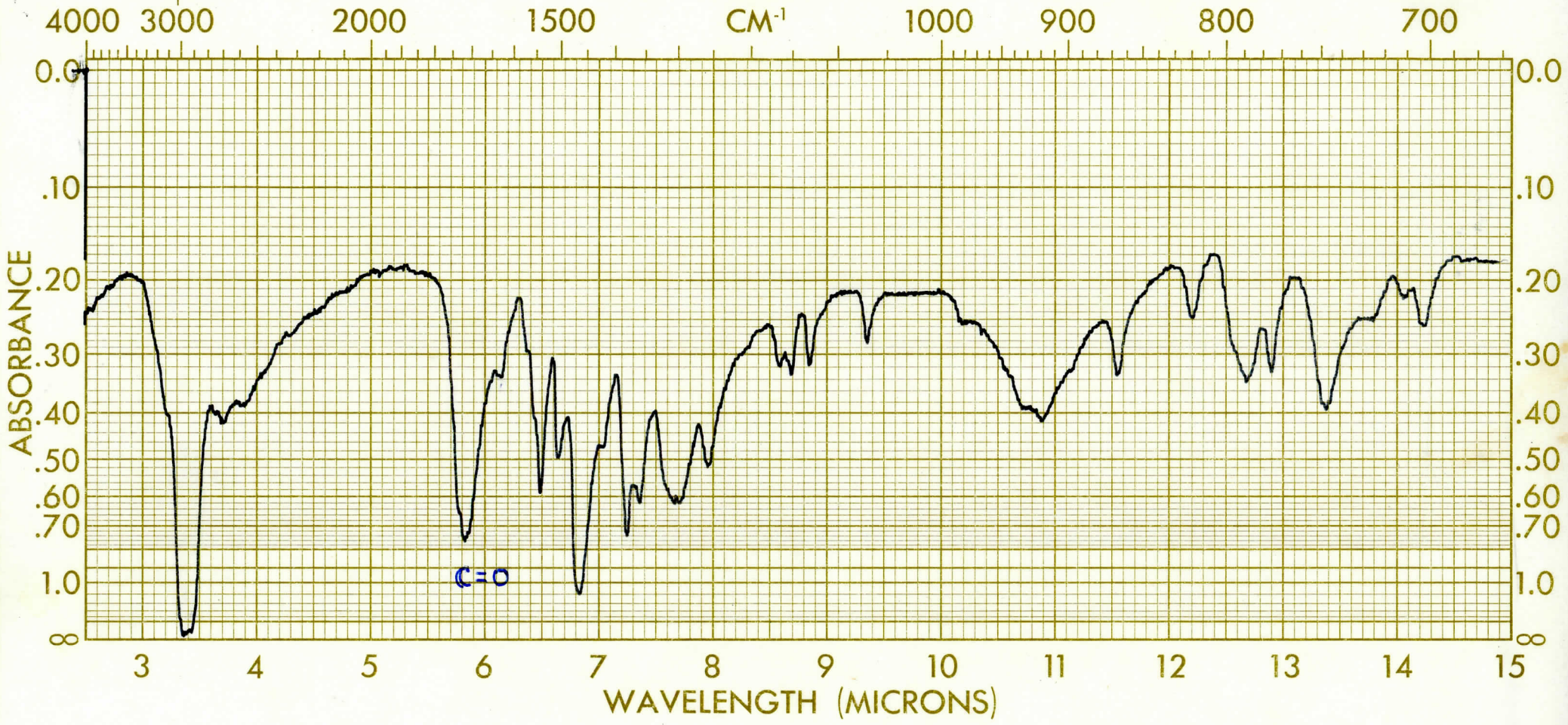
Experimental: 50 ml of concentrated sulfuric acid is poured into a one liter round bottom flask. The flask is placed in ice and 50 ml of 60% fuming sulfuric acid is added in small portions with stirring after each addition over a period of fifteen minutes. The temperature rises to approximately 50°C. The solution is cooled to approximately 30°C, and 100 ml of concentrated nitric acid is added very slowly in small portions with stirring after each addition. The reaction is very exothermic for the first 20 to 30 ml and the temperature rises to approximately 70°C. For subsequent additions the reaction is less exothermic. The nitration mix is cooled to 40°C. The terephthalic acid is added and forms a slurry. The mixture is heated on a water bath for one and one half hours. During this time the temperature is maintained at approximately 50°C.

The mixture is then heated on a sand bath until it boils and voluminous oxides of nitrogen are evolved. The temperature is 70°-90°C. Complete solution is never attained. The mixture is allowed to stand and digest for four to six hours. It is poured over ice and diluted to one liter with water. The white crystalline product of nitro terephthalic acid is filtered off, washed two times with 75 ml of water, and dried. The crude yield is 22 grams which is 87% theoretical. The nitro terephthalic acid can be recrystallized from hot water, but the crude product is sufficiently pure to make this step unnecessary. If recrystallized, the yield is 77% theoretical. The melting point of the crude material is 260-5°C, while that of the recrystallized product is 270-1°C. The values recorded in the literature are: 262-3[7] and 270[8]. Infra red spectrum of nitro terephthalic acid: Exp. #525 Step I (1) 10/4/62.

Preparation of amino terephthalic acid:

Attempts were first made to reduce nitro terephthalic acid with stannous chloride and hydrochloric acid and with tin and hydrochloric acid. These procedures led to the formation of salts and made isolation of the desired product difficult. Reduction of the nitro terephthalic acid to amino terephthalic acid with $Na_2S_2O_4$ in an alkaline medium proved to be a far superior method of preparation.[9]

Experimental: 22 grams of crude nitro terephthalic acid is placed in 400 ml of water and stirred to form a slurry. 10%



SPECTRUM NO. #1

SAMPLE Nitrotetrephthalic acid

made Oct 4, 1962

ORIGIN Exp 525 Step 1 (1)

Yield 1.2 gms RX from hot HOH

PURITY MP 269-270 uncorr

PHASE Nujol mull

THICKNESS D.M.

LEGEND

1.

2.

DATE 10/4/62

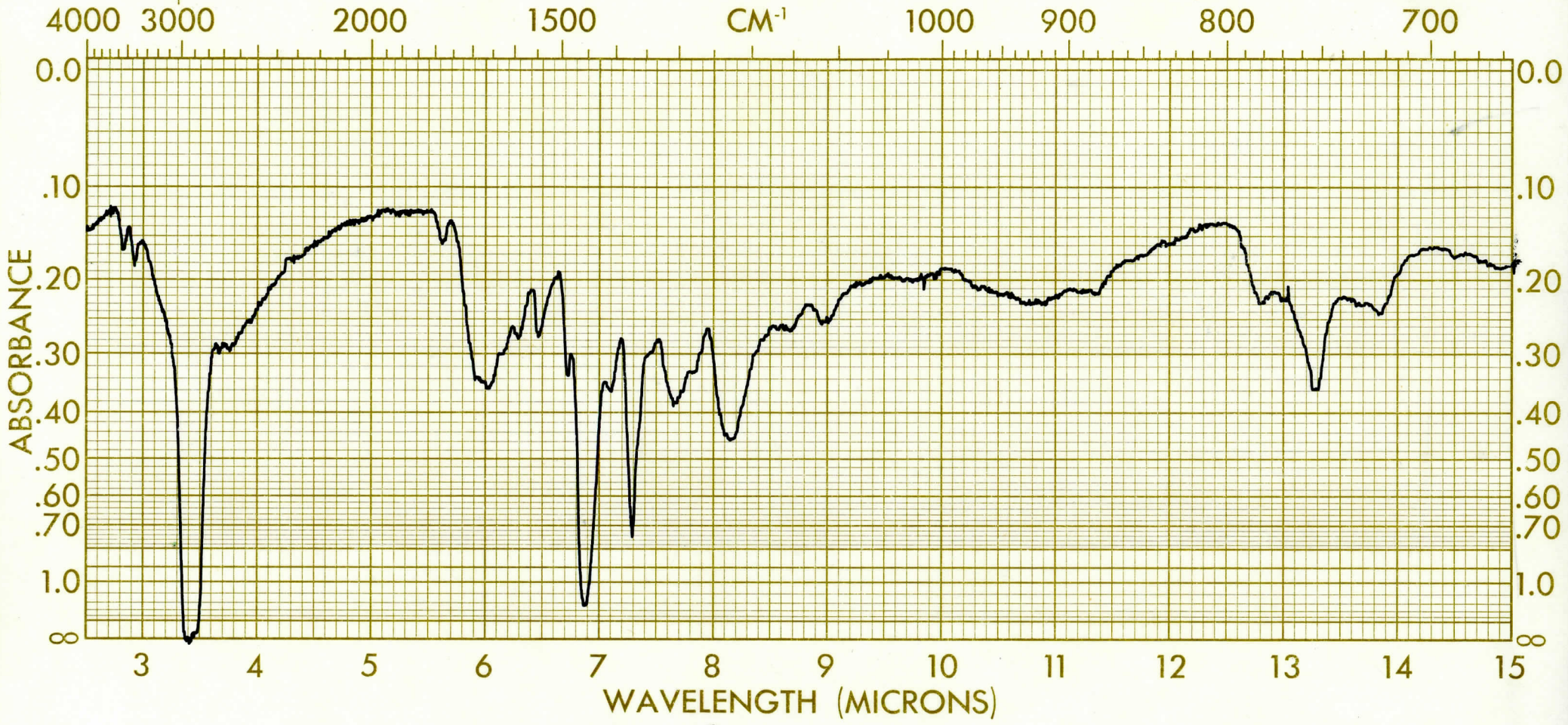
OPERATOR E.M. Joule

REMARKS

SPECTRUM NO.

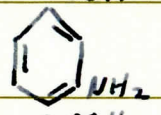
SAMPLE

sodium hydroxide solution is added to the slurry until it is strongly basic to pH paper. This required 300-400 ml of NaOH solution. All the solids dissolve. The solution is heated to 80°C, and 48 grams of $Na_2S_2O_4$ are added over a period of 20 minutes. The pH is checked at frequent intervals, and 10% NaOH solution is added when necessary to keep the solution basic. After all the $Na_2S_2O_4$ has been added the reaction mix is heated at 80°C for an additional half hour. The solution is cooled and filtered. A 1:1 sulfuric acid and water solution is added to the yellow reaction mix until the pH is approximately 4. A thick yellow precipitate separates and is filtered off by suction. The paste-like precipitate is suspended in 400 ml of water to wash it free from acids and salts and filtered again by suction. The amino terephthalic acid is dried, forming a hard cake which must be ground into a powdered form for use in the next step. The crude yield is 11.7 grams or 62% of the theoretical. The crude amino terephthalic acid is used in the preparation of 7-carboxy isatoic anhydride. It can be recrystallized from hot water. However, this is difficult because amino terephthalic acid is only very slightly soluble in hot water. This material shows blue fluorescence in solution. The melting point of the recrystallized material is 324-5°C. This compared favorably with the literature value of 325°C[10]. Infra red spectrum of amino terephthalic acid: Exp. #525 Step II (6) #1 11/19/62 2:15 PM.



SPECTRUM NO. #1

SAMPLE Amino Tere-phthalic acid



ORIGIN #525 2-6 11/8/62

PURITY Rx from hot HOH

PHASE Nujol Mull

THICKNESS O.M.

LEGEND

1.

2.

DATE 11/19/62 2:15 P.M.

OPERATOR EM Jonle

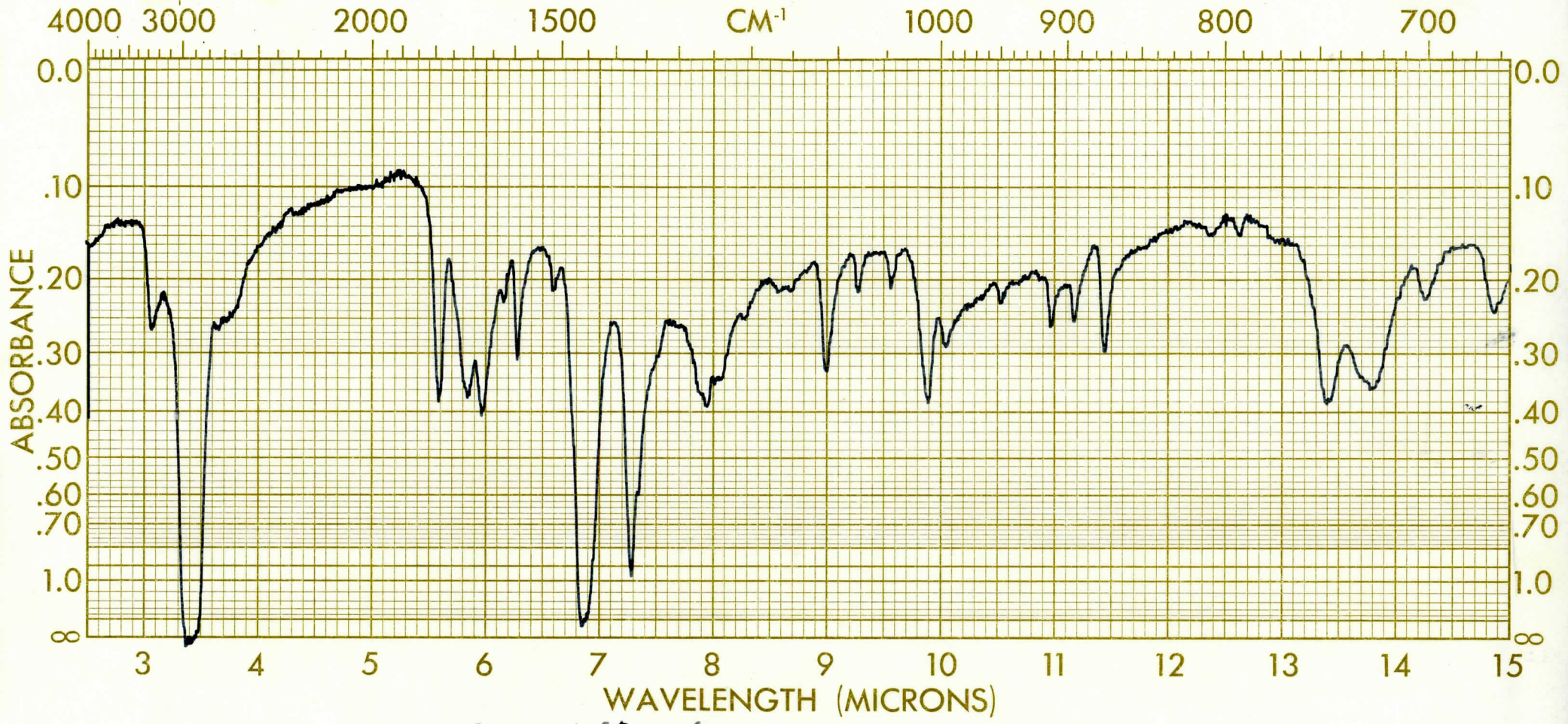
REMARKS Vial samples

SPECTRUM NO.
SAMPLE

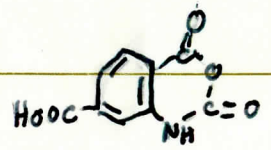
Synthesis of 7-Carboxy Isatoic Anhydride

Experimental: 7-carboxy isatoic anhydride was first prepared according to the procedure described for isatoic anhydride by Wagner and Fegley[11]. Amino terephthalic acid was dissolved with difficulty in strong HCl solution. Phosgene was bubbled into the solution, and upon standing a small amount of cream colored precipitate separated. This precipitate was filtered off, and more phosgene was bubbled into the filtrate. After standing, another small amount of cream colored precipitate separated and was filtered off and dried. Infra red spectra showed these two yields to be the same product.

Attempts were made to recrystallize the product from various solvents. Water was first tried and proved to be unsuitable because when the product was boiled in water it was partially reconverted to amino terephthalic acid. Benzene also proved to be a poor solvent because the product was almost insoluble even at the boiling point. The most suitable solvent tried was dioxane, and an amount of product sufficient for analysis was obtained. The carbon and hydrogen analysis confirmed this product to be 7-carboxy isatoic anhydride. The theoretical values were carbon 52.2%, hydrogen 2.78%; and the percentages found were: carbon 52.3% and hydrogen 2.98%. 7-carboxy isatoic anhydride when recrystallized from dioxane with charcoal is a white powder which does not melt below 340°C. (Infra red spectra Exp. #525 Step III (3) #3 11/6/62 4:00 PM.) Although the product was recrystallized from dioxane, dioxane is not an ideal solvent



Exp 525 Step 3 (3)

SPECTRUM NO. #3	ORIGIN ~~7(3) #3, 11/30/62~~	LEGEND	REMARKS
SAMPLE 7-Carboxy I.A.		1.	
	PURITY Rx from Dioxane	2.	
	PHASE Nujol Mull	DATE 11/6/62 4:PM	
	THICKNESS O.M.	OPERATOR EMJ	

SPECTRUM NO. _____ SAMPLE _____

for the recrystallization of 7-carboxy isatoic anhydride because of its moderate solubility at high temperatures and reprecipitation is slow. If fast reprecipitation is desired water must be added to the dioxane solution.

Preparation of 7-carboxy isatoic anhydride by bubbling phosgene into a hydrochloric acid solution of amino terephthalic acid has many undesirable aspects. Amino terephthalic acid is only very slightly soluble in water and in hydrochloric acid solution. Therefore a very large amount of solvent must be used. The solubility of 7-carboxy isatoic anhydride is nearly the same as that of amino terephthalic acid and it does not separate readily from solution.

In an attempt to eliminate these undesirable features from the preparation, dioxane was tried as a solvent. Amino terephthalic acid was found to be slightly more soluble in dioxane than in hydrochloric acid solution (about one gram/100 ml of dioxane). A saturated dioxane solution of amino terephthalic acid was prepared, and phosgene was bubbled into the solution through a sintered glass disperser until the solution was saturated with phosgene. A small amount of precipitate separated upon standing. A larger recovery of 7-carboxy isatoic anhydride can be obtained by vacuum distilling the dioxane solvent. By this procedure a 96% crude yield is obtained.

An alternate procedure[12] for the preparation of 7-carboxy isatoic anhydride in dioxane as a solvent was developed. A slurry of amino terephthalic acid and dioxane is made using 10 ml of

dioxane per gram of amino terephthalic acid. Two moles of phosgene are bubbled into the mixture for each mole of amino terephthalic acid present. The reaction mixture is then refluxed gently with frequent stirring for half an hour. After the mixture has cooled it is poured into ice and water and the cream colored precipitate is filtered off, washed two times and dried. The yield 7-carboxy isatoic anhydride by this method of preparation is 87% theoretical.

Reactions of 7-Carboxy Isatoic Anhydride

Common nucleophilic agents attack the number four carbon atom in 7-carboxy isatoic anhydride as in unsubstituted isatoic anhydride. Electrons are withdrawn from both the number two and the number four carbon atoms by the carbon atoms by the carbonyl oxygen atoms. The high electron density of the nitrogen atom, however, partially compensates for the positive character of the number two carbon atom. Therefore the number four carbon atom is attacked by the nucleophile. Although 7-carboxy isatoic anhydride undergoes the same reactions as unsubstituted isatoic anhydride it does not appear to be as reactive. The formation of esters and thio esters by reaction with alcohols and thio alcohols occurs quite easily with unsubstituted isatoic anhydride requires vigorous conditions when 7-carboxy isatoic anhydride is used, and these products are difficult to make. Although the formation of amides, anilides, and hydrazides from 7-carboxy isatoic anhydride is quite easy these reactions also do not occur as readily with unsubstituted isatoic anhydride.

Synthesis of 2-Amino-4-Carboxy Methyl Benzoate

Experimental: One gram of 7-carboxy isatoic anhydride is dissolved in 10 ml of methyl alcohol, and a chip of sodium hydroxide is added as a catalyst. The reaction mixture is refluxed for five hours. The solution turns yellow and shows a blue fluorescence characteristic of anthranilates. The solvent is partially evaporated and a yellow precipitate forms. The crude product is recrystallized two times from methanol. 2-amino-4-carboxy methyl

benzoate is rather soluble in methanol and only a small amount of solvent is needed for recrystallization.

Recrystallized 2-amino-4-carboxy methyl benzoate is a yellow crystalline solid with a melting point of 214-7°C. The analysis for this compound was as follows: theoretical carbon 55.38%, hydrogen 4.65%; found carbon 55.05%, hydrogen 4.&2%. Infra red spectra: Experiment #531(5) #2, 2/4/63 3:30PM.

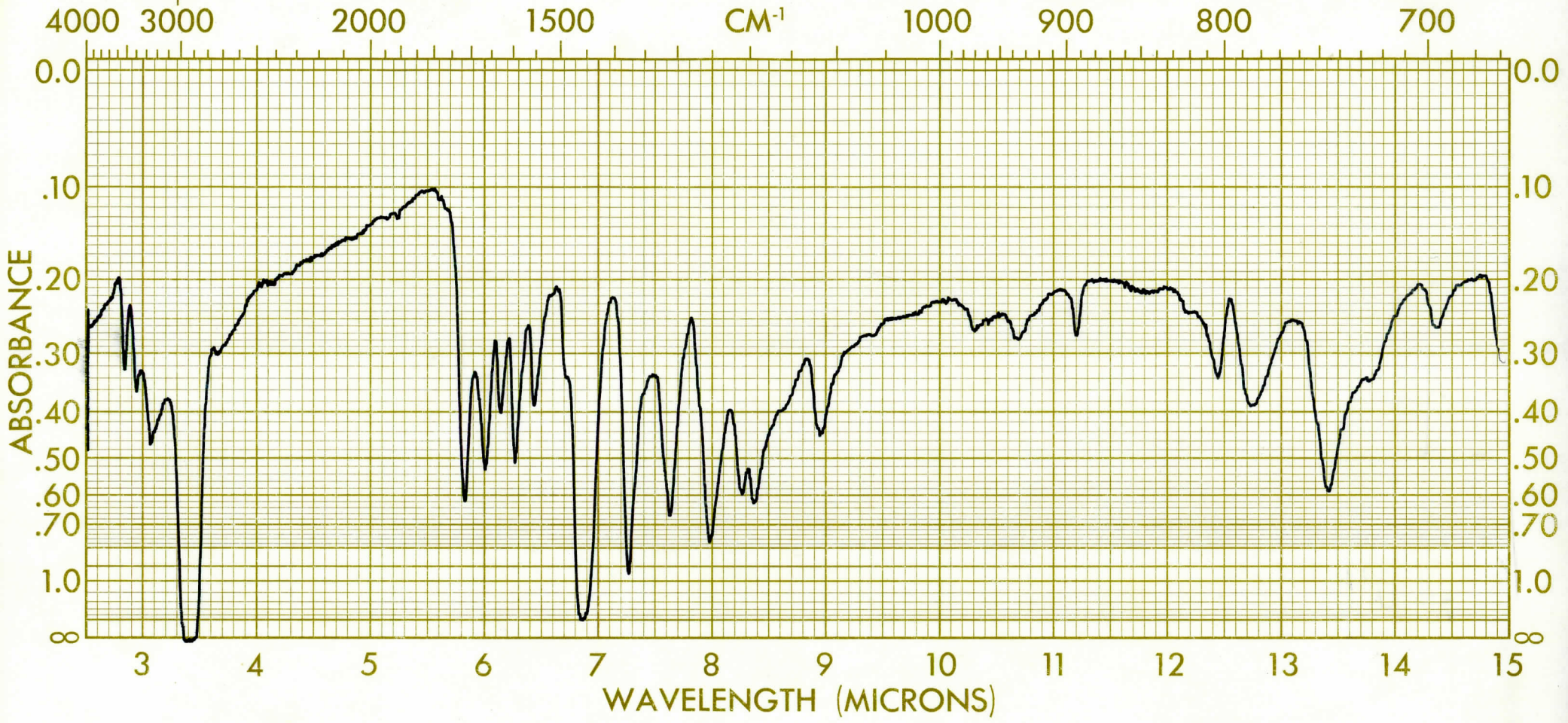
Synthesis of 2-Amino-4-Carboxy Thio Phenyl Benzoate

Experimental: A slurry is made of one gram of 7-carboxy isatoic anhydride and 10 ml of dioxane. Five ml of thio phenol and a chip of sodium hydroxide, which acts as a catalyst in the reaction, are added to the slurry. The reaction mixture is refluxed for half an hour. The solution is cooled and upon standing a precipitate separates. The precipitate is filtered off and recrystallized from methanol.

2-amino-4-carboxy thio phenyl benzoate is a yellow crystalline solid with a melting point of 238-40°C. The analysis for this compound is as follows: theoretical carbon 61.52%, hydrogen 4.06%; found carbon 61.37%, hydrogen 4.13%. Infra red spectra: Experiment #547(1) #2 3/19/63 3:15PM.

Synthesis of 2-Amino-4-Carboxy Benzamide

Experimental: One gram of 7-carboxy isatoic anhydride is mixed with 10 ml of water. A 50% solution of NH_4OH in water is added dropwise to this mixture, and an orange solution is formed. This solution is heated and carbon dioxide evolution is noted.



SPECTRUM NO. #2

SAMPLE 2 amino. 4 - carboxy methyl benzoate

ORIGIN Expo 531 Steptec (S)

MP 213-217

PURITY RX from MeOH

PHASE Nujol Mull

THICKNESS D.M.

LEGEND

1.

2.

DATE Feb. 4, 1963 3:30PM.

OPERATOR E.M.J.

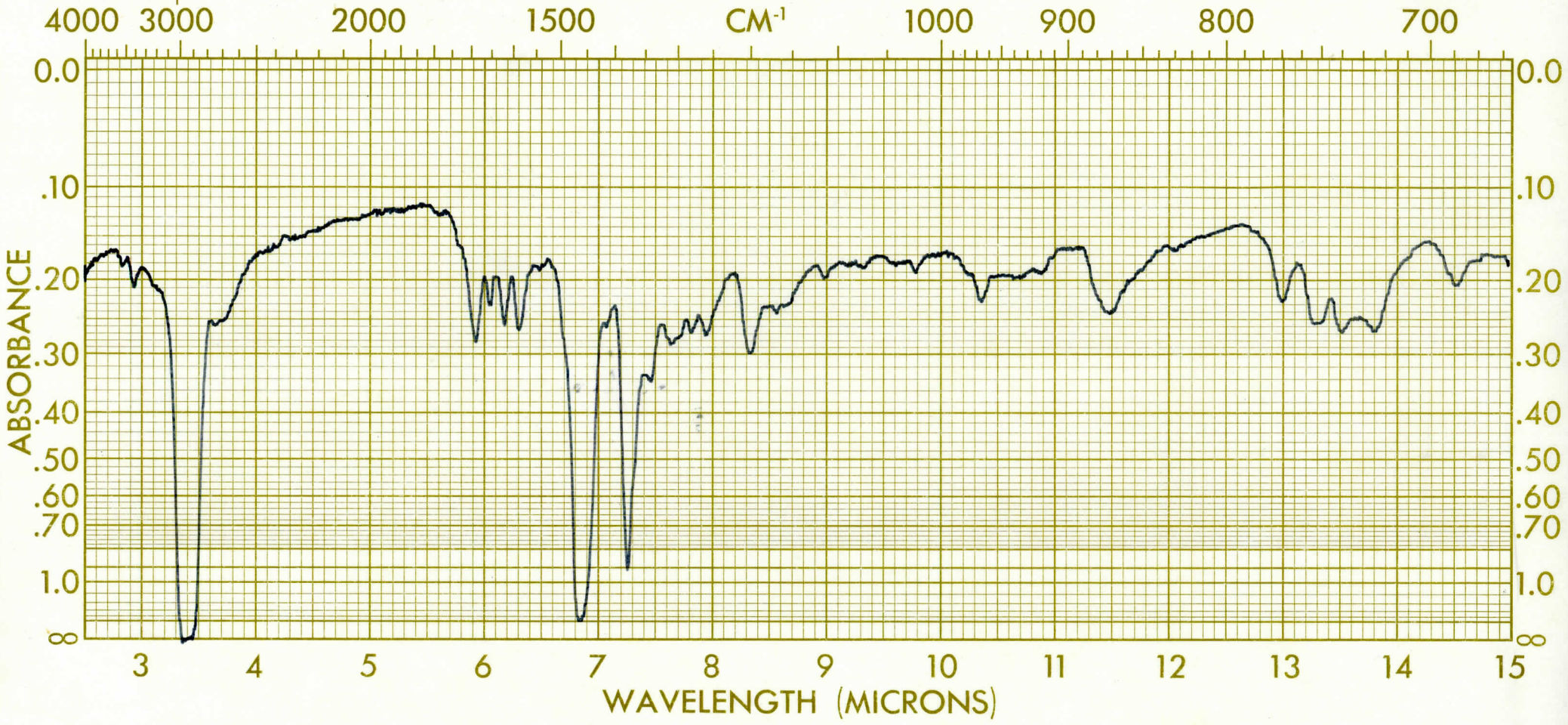
REMARKS

Analysis

	Theo	Found
C	55.38	56.05
H	4.65	4.72

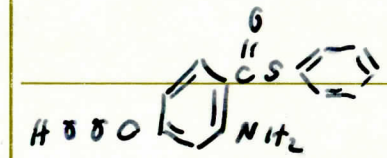
SPECTRUM NO.

SAMPLE



SPECTRUM NO. #2

SAMPLE



2 amino 4 carboxy phenyl thio benzoate

ORIGIN 547 C1)

MP 238-240

PURITY Rx MeOH

PHASE Nujol Mull

THICKNESS D. M.

LEGEND

1.

2.

DATE 3/19/63 3:15PM.

OPERATOR EM Joule

REMARKS Appears to be desired product.

Analysis

	Theo	Found
C	61.52	61.37
H	4.06	4.13

SPECTRUM NO.

SAMPLE

The solution is cooled and acicified with acetic acid. A yellow precipitate separates and is filtered and dried. This product can be recrystallized form a 50% water-ethanol solution.

2-amino-4-carboxy benzamide is a yellow powder which melts above 240°C. The analysis of this product is as follows: theoretical carbon 53.33%, hydrogen 4.44%; found carbon 53.25%, hydrogen 4.41%. Infra red spectra: Experiment #532(3) #1 2/18/63 1:30PM.

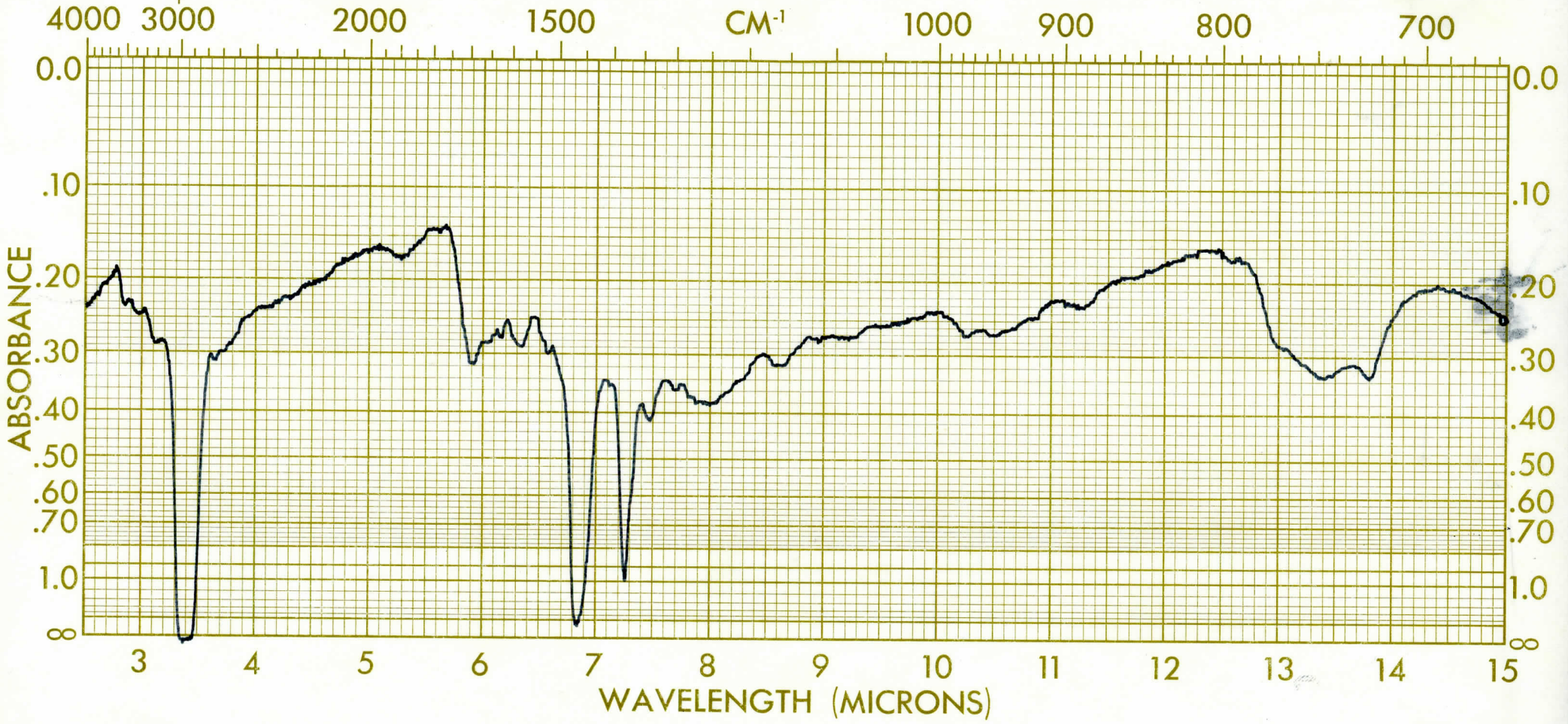
Synthesis of 2-Amino-4-Carboxy Benzanilide

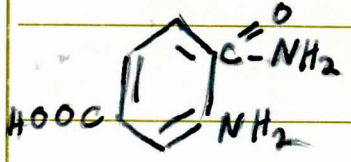
Experimental: One gram of 7-carboxy isatoic anhydride is mixed with dioxane, which is used as a solvent. 0.9 ml of aniline is added. This represents a two to one molar ratio of aniline to 7-carboxy isatoic anhydride. The reaction mixture is refluxed for 3/4hour. When the mixture is cooled no precipitate separates; therefore the solvent is evaporated. The product is recrystallized two times from a one to two solution by volume of methanol and water.

2-amino-4-carboxy benzanilide when recrystallized from methanol and water using charcoal is a white powder which melts 233-4°C. The analysis is as follows: theoretical carbon 65.63%, hydrogen 4.72%; found carbon 65.65%, hydrogen 4.84%. Infra red spectra: Experiment #535(1) 2/19/63 2:15 PM.

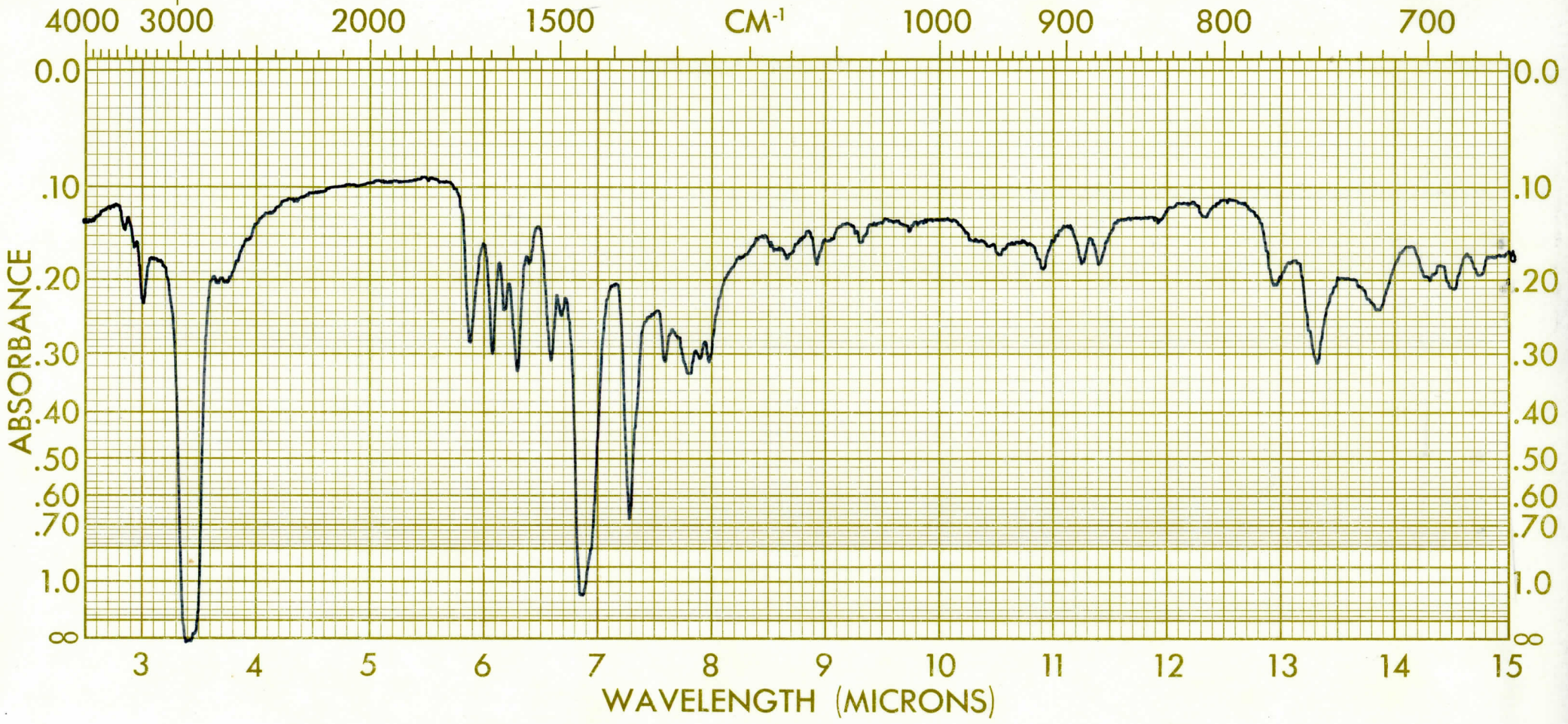
Synthesis of 2-Amino-4-Carboxy N-Hexylbenzamide

An attempt was made to prepare 2-amino-4-carboxy N-hexyl benzamide by refluxing 7-carboxy isatoic anhydride with



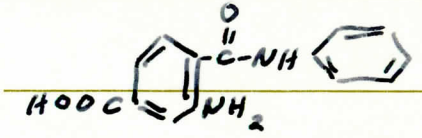
SPECTRUM NO. #1	ORIGIN 538(3)	LEGEND	REMARKS
SAMPLE 2-amino, 4-carboxy benzamid		1.	
	PURITY Crude	2.	
	PHASE Nujol Mull	DATE 2/18/63 1:30PM	
	THICKNESS N.M.	OPERATOR EM Jaude	

SPECTRUM NO. ____ SAMPLE ____



SPECTRUM NO. #5

SAMPLE 2-amino 4-carboxy benzanilide



ORIGIN Exp 636(1)

R2 1:2 MeOH:H2O

PURITY MP 233-234

Nujol Mull

PHASE

THICKNESS D.M.-

LEGEND

1.

2.

DATE 2/19/63 2:15PM

OPERATOR E.M. Jule

REMARKS

Sent for analysis

	Theo	Found
C	65.62	66.65
H	4.72	4.84

SPECTRUM NO.

SAMPLE

an excess of n-hexyl amine in dioxane, which was used as a solvent. The solvent was evaporated and the product recrystallized from a one to one methanol and water solution. Light fluffy white needle like crystals with a melting point 139.5-40°C. were obtained. Three sets of analyses were obtained for this compound. They are as follows:

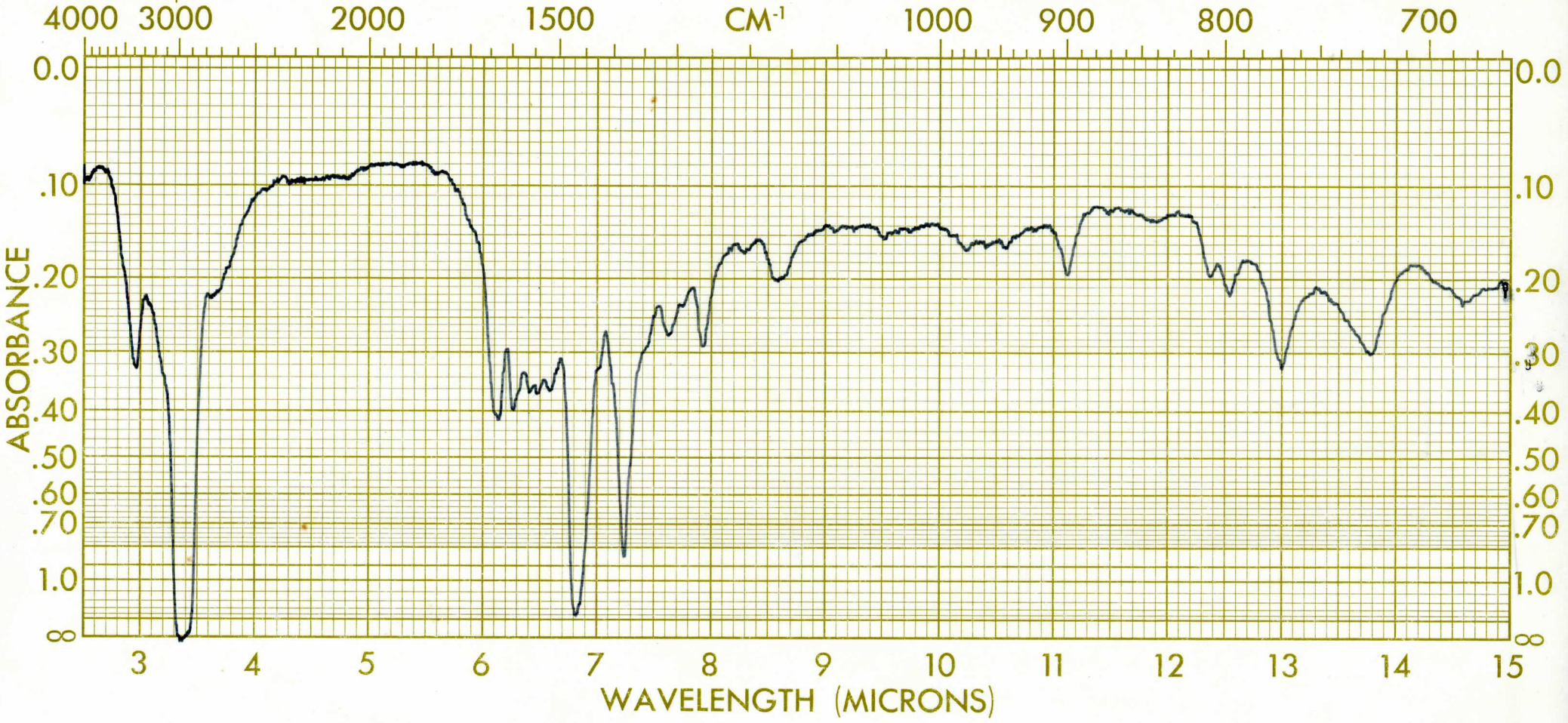
	Theoretical		Found	
C	63.61%	63.07%	62.71%	64.88%
H	7.63%	9.67%	9.77%	9.72%

The infra red spectra of this material is Experiment #536(1) #3 2/28/63 10:00AM. This material is probably an unstable amine salt of the 2-amino-4-carboxy N-hexyl benzamide. This would explain the variation in analysis. The high solubility of this compound in water is also consistant with this hypothesis.

If this compound is dissolved in water and the solution acidified a new procipitate forms. This new product can be recrystallized from a one to one solution of methanol and water. It is a white powder which melts 172-3°C. This product is believed to be the 2-amino-4-carboxy N-hexyl benzamide. Infra red spectra: Experiment #536(3) #1 4/19/63 3:00 PM.

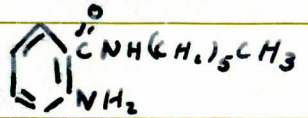
Synthesis of 2-Amino-4-Carboxy Benzhydrazide

Experimental: One gram of 7-carboxy isatoic anhydride is suspended in 10 ml of water. A one to one solution of hydrazine in water is added dropwise until the solution is slightly basic. There is considerable evolution of carbon dioxide. A yellow solution is formed when the mixture is heated. Enough hydrazine



SPECTRUM NO. #3

SAMPLE 2 amino, 4 carboxy N hexyl benzamid



ORIGIN Exp 536 (1)

MP 139.5 - 140.0

PURITY RX 2nd time hot HOH

PHASE Nujol Mull

THICKNESS 0.M.

LEGEND

1.

2.

10:00 AM

DATE 2/28/63

OPERATOR E.M. Joule

REMARKS Sent for analysis

	Theo	Found	
C 168.14	63.61%	63.07	62.77
H 20.16	7.63%	8.06	7.77
N 28.02			
O 48.00			
MW 264.32			

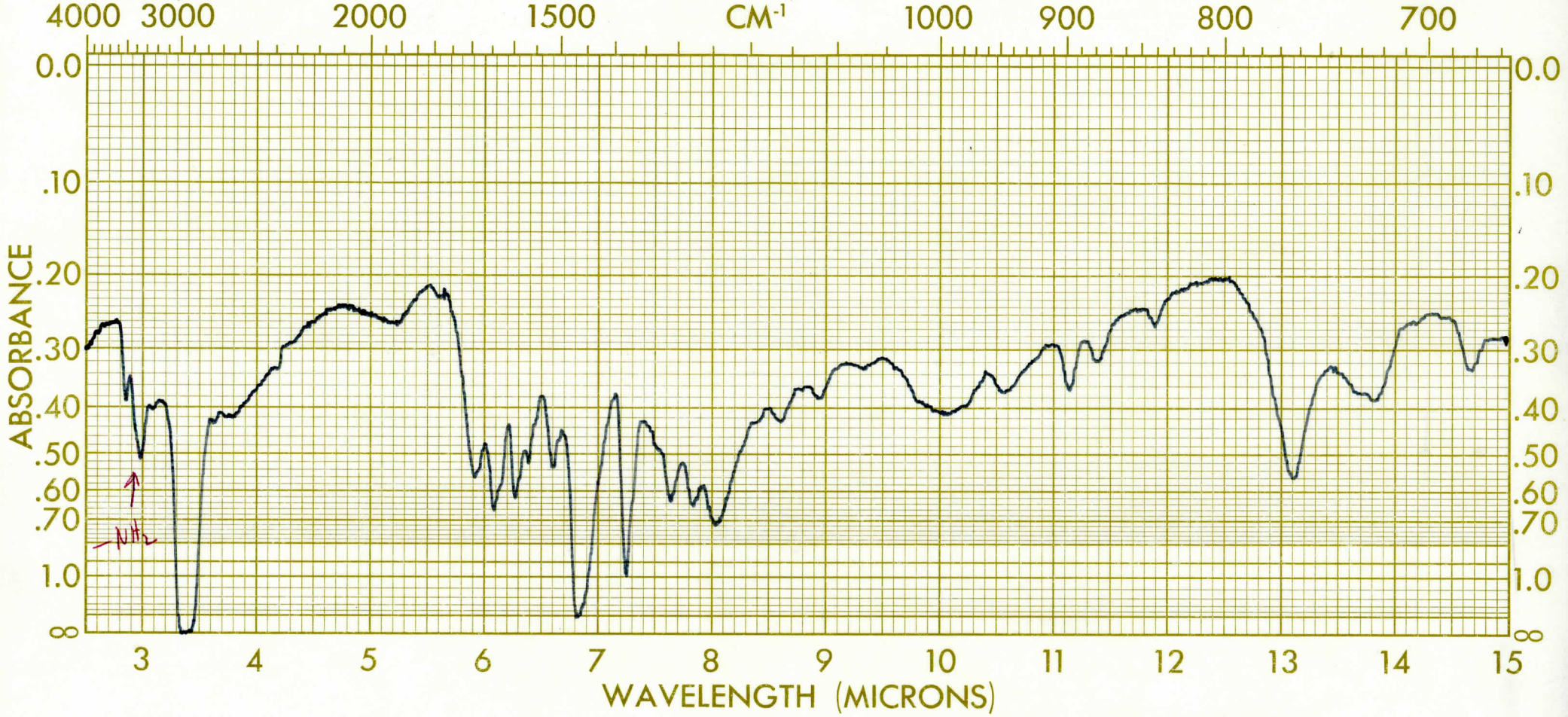
SPECTRUM NO. ____ SAMPLE ____

solution is added during the heating to keep the reaction mixture basic. After 15 minutes of heating the solution is cooled and acidified with 30% acetic acid. A yellow precipitate forms and is filtered. The product is recrystallized two times using a one to one solution of methanol and water.

2-amino-4-carboxy benzhydrazide is a fluffy yellow crystalline solid with a melting point of 235.5-236.5°C. The analysis is as follows: theoretical carbon 49.23%, hydrogen 4.65%; found carbon 49.07%, hydrogen 4.70%. Infra red spectra: Experiment #538(1) #4 3/12/63 10:00 AM.

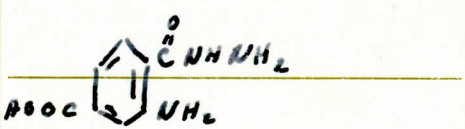
Synthesis of 2-Amino-4-Carboxy N'-Phenyl Benzhydrazide Experimental: One gram of 7-carboxy isatoic anhydride is suspended in 10 ml of water. The mixture is heated and phenylhydrazine is added dropwise. Carbon dioxide evolves, and the precipitate changes character. The mixture is cooled and the product filtered. The 2-amino-4-carboxy N'-phenyl benzhydrazide is recrystallized from a one to one solution by volume of methanol and water.

2-amino-4-carboxy N'-phenyl benzhydrazide is a cream colored powder which melts at 205.5-206.5°C. The analysis is as follows: theoretical carbon 62.00%, hydrogen 4.81%; found carbon 61.88%, hydrogen 4.82%. Infra red spectra: Experiment #546(3) #4 4/8/63 2:30PM.



SPECTRUM NO. #4

SAMPLE



2 amino, 4 carboxy benzhydrazide

ORIGIN Exp 538 (1) 3/4/63.

RX 2x 1:1 H_2O:MeOH

PURITY M.P. 235.5-236°

PHASE Nujol Mull

THICKNESS D.M.

LEGEND

1.

2.

DATE 3/12/63 10:AM

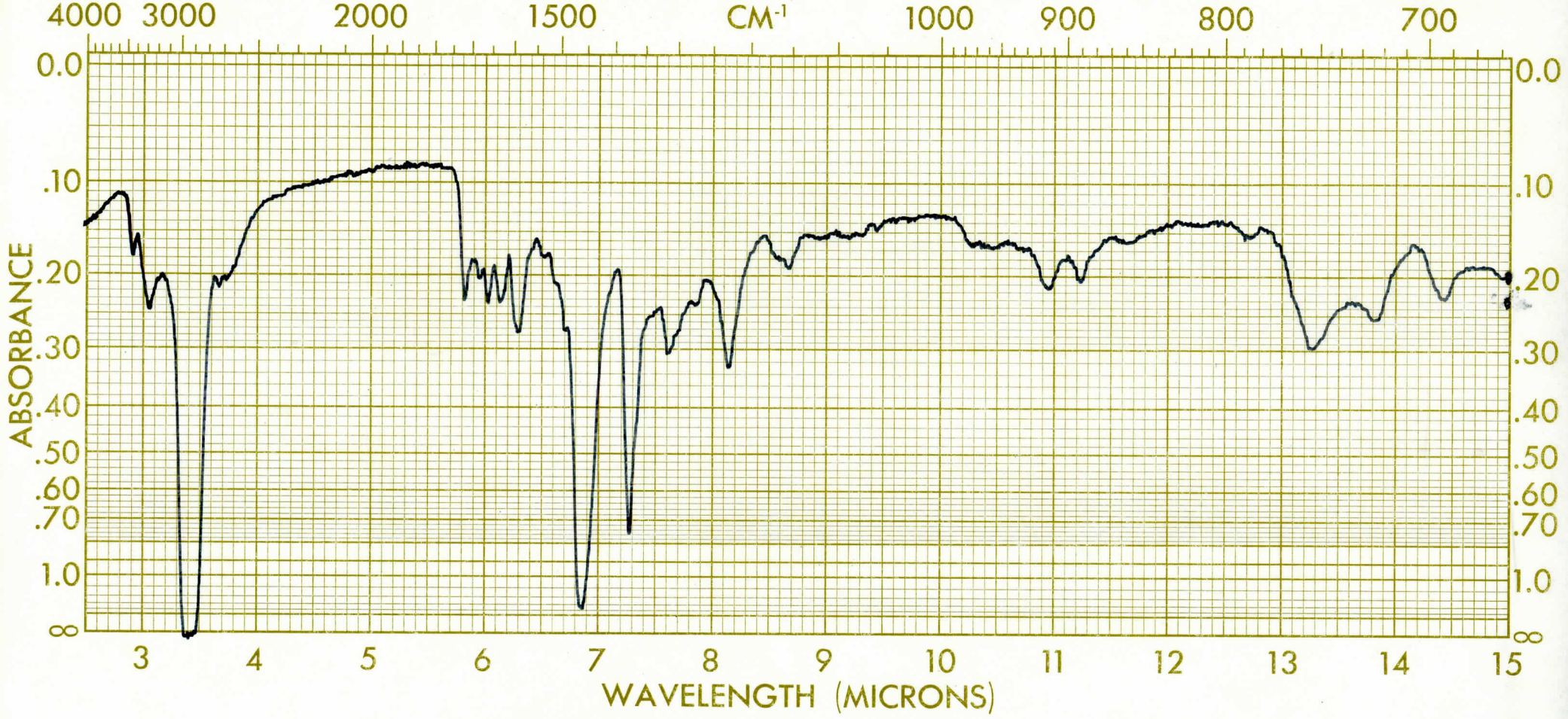
OPERATOR E.M. Soule

REMARKS

Analysis	Theo	Found
C = 96.08	49.23	49.07
H 9.07	4.66	4.70
O 48.00		
N 42.02		

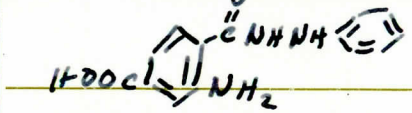
MW = 195.17

SPECTRUM NO. SAMPLE



SPECTRUM NO. #4

SAMPLE 2-amino-4-carboxy N'phenyl benz hydrazide



ORIGIN Exp# 546(3)

MP 205.5-206.5°

PURITY RX 2x 1:1 MeOH:H2O

PHASE Nujol Mull

THICKNESS O.M.

LEGEND

1.

2.

DATE 4/8/63 2:30PM.

OPERATOR E.M. Janke

REMARKS Sample sent for analysis

C	Theo	Found
C	62.0	61.88
H	4.91	4.82

SPECTRUM NO.

SAMPLE

Summary

1. 7-Carboxy isatoic anhydride is prepared by nitrating terephthalic acid to form nitro terephthalic acid, reducing the nitro group to form amino terephthalic acid, and closing the ring with phosgene to form the desired product.

2. 7-Carboxy isatoic anhydride is attacked by common nucleophiles as is unsubstituted isatoic anhydride, but the 7-carboxy isatoic anhydride is less reactive than the unsubstituted isatoic anhydride.

Footnotes

1. Beilsteins Handbuch der Organische Chemie, IX, 851
2. ibid. XIV, 558
3. Roger P. Staiger and Emery B. Miller, Journal of Organic Chemistry, XXIV, 1214 (1959)
4. Beilsteins Handbuch der Organische Chemie, IX, 851
5. Wegscheider, Monatshefte für Chemie, XXI, 623
6. Skraup and Brunner, Monatshefte für Chemie, VII, 147
7. Wegscheider, Monatshefte für Chemie, XXI, 623
8. Burkhardt, Berichte der Deutschen Chemischen Geselschaft, X, 145
9. Unpublished works of Roger P. Staiger, Experiment 487
10. Heilbron, Dictionary of Organic Compounds, I, 139
11. E. C. Wagner and M. F. Fegley, Organic Synthesis Collective Volume III, 488(1955)
12. Unpublished works of Roger P. Staiger.

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